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Cirrhosis associated with decreased survival and a 10-year lower median age at death of cystic fibrosis patients in the Netherlands

Pals, F.H.; Verkade, H J; Gulmans, V A M; De Koning, B A E; Koot, B G P; De Meij, T G J; Hendriks, D M; Gierenz, N; Vreugdenhil, A C E; Houwen, R H J

Published in:
Journal of Cystic Fibrosis

DOI:
[10.1016/j.jcf.2018.11.009](https://doi.org/10.1016/j.jcf.2018.11.009)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Pals, F. H., Verkade, H. J., Gulmans, V. A. M., De Koning, B. A. E., Koot, B. G. P., De Meij, T. G. J., Hendriks, D. M., Gierenz, N., Vreugdenhil, A. C. E., Houwen, R. H. J., & Bodewes, F. A. J. A. (2019). Cirrhosis associated with decreased survival and a 10-year lower median age at death of cystic fibrosis patients in the Netherlands. *Journal of Cystic Fibrosis*, 18(3), 385-389.
<https://doi.org/10.1016/j.jcf.2018.11.009>

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Title page

CIRRHOSIS ASSOCIATED WITH DECREASED SURVIVAL AND A 10-YEAR
LOWER MEDIAN AGE AT DEATH OF CYSTIC FIBROSIS PATIENTS IN THE
NETHERLANDS

Pals, FH ¹,
Verkade HJ ¹,
Gulmans VAM²,
de Koning BAE ³,
Koot BGP ⁴,
de Meij TGJ ⁵,
Hendriks DM ⁶,
Gierenz N ⁷,
Vreugdenhil ACE⁸,
Houwen RHJ ⁹,
Bodewes FAJA¹

¹ The University Medical Center Groningen, Dept. of Pediatrics, University of Groningen, Groningen, the Netherlands
Hanzeplein 1
9713 GZ Groningen
The Netherlands
f.h.pals@umcg.nl; h.j.verkade@umcg.nl; f.a.j.a.bodewes@umcg.nl

² Dutch Cystic Fibrosis Foundation (NCFS), Baarn, the Netherlands
Doctor Albert Schweitzerweg 3
3744 MG Baarn
The Netherlands
V.Gulmans@ncfs.nl

³ Erasmus University Medical Center, Rotterdam, the Netherlands
Dr, Doctor Molewaterplein 40
3015 GD Rotterdam
The Netherlands

b.dekoning@erasmusmc.nl

⁴Academic Medical Center, Amsterdam, the Netherlands
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands
b.g.koot@amc.uva.nl

⁵ VU University Medical Center, Amsterdam, the Netherlands
De Boelelaan 1117
1081 HV Amsterdam
The Netherlands
t.demeij@vumc.nl

⁶Haga Hospital, The Hague, the Netherlands
Els Borst-Eilersplein 275
2545 AA Den Haag
The Netherlands
d.hendriks@hagaziekenhuis.nl

⁷Radboud University Medical Center, Nijmegen, the Netherlands
Geert Grooteplein Zuid 10
6525 GA Nijmegen
The Netherlands
N.Gierenz@cukz.umcn.nl

⁸ Maastricht University Medical Center, Maastricht, the Netherlands
P. Debyelaan 25
6229 HX Maastricht
The Netherlands
A.vreugdenhil@mumc.nl

⁹Department of Pediatric Gastroenterology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands
Lundlaan 6
3584 EA Utrecht
The Netherlands
r.houwen@umcutrecht.nl

Conflicts of interest: none

Corresponding author:

F.A.J.A. Bodewes, MD, PhD
University Medical Center Groningen
Hanzeplein 1
9713GZ Groningen
The Netherlands
f.a.j.a.bodewes@umcg.nl

Presentation

Study recently presented at the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) annual meeting 2018, Geneva. 11th May, plenary session, oral.

Abstract

Background

Up to 10% of patients with Cystic Fibrosis develop cirrhotic CF-related liver disease with portal hypertension: CF cirrhosis (CFC). In a nationwide study, we aimed to determine the role of CFC on survival in the Netherlands between 1-1-2009 and 1-1-2015.

Methods

We identified all CFC patients in the Netherlands, based on ultrasonographic liver nodularity and portal hypertension. A non-cirrhotic control group was obtained from the national Dutch CF patient registry. We compared groups with regards to baseline lung function and nutritional status and survival and age at death over a 6-year period. In case of death of CFC patients, the clinical reported cause was recorded.

Results

At baseline, we found no significant difference in lung function and nutritional status between the CFC patients (N=95) and controls (N=980). Both the 6-year survival rate (77 vs. 93%; $P < .01$) and the median age at death (27 vs. 37 years; $P = .02$) was significantly lower in CFC compared to controls. In the deceased CFC patients, the reported primary cause of death was pulmonary in 68% of cases, and liver failure related in 18% of cases.

Conclusions

In the Netherlands, the presence of CFC is associated with a higher risk for early mortality and an approximately 10-year lower median age at death. This substantial poorer outcome of CFC patients was not reflected in a lower baseline lung function or a diminished nutritional status. However, in the case of mortality, the reported primary cause of death in CFC patients is predominantly pulmonary failure and not end-stage liver disease.

Highlights

- Cystic fibrosis related cirrhosis (CFC) is associated with decreased survival rates in CF patients
- Presence of CFC in CF patients is associated with a 10-year lower median age at death in CF patients.
- Reported cause of death in CFC patients was predominantly pulmonary failure

- Elective surgery is a potential risk factor for the progression of stable cirrhosis into acute-on-chronic liver failure

Keywords

- Cystic fibrosis
- Cirrhosis
- Survival rate
- Cause of death
- Pulmonary function
- Nutritional status

Abbreviations

BMI: Body mass index

CFC: Cystic fibrosis related cirrhosis

CF: Cystic fibrosis

CFLD: Cystic fibrosis related liver disease

DIOS: distal intestinal obstruction syndrome

IQR: interquartile range

FEV1%: best registered forced Expiratory Volume in the 1st second as percentage of predicted value for age, height and gender

FVC%: best registered vital capacity as percentage of predicted value for age, height and gender

Introduction

Cystic Fibrosis cirrhosis

Cystic Fibrosis is a common genetic disease with a worldwide incidence of approximately 1 in 3000 live births.(1) Besides the severe progressive pulmonary disease, cystic fibrosis cirrhosis (CFC) could be a common cause of morbidity in CF patients.(2) The reported prevalence of CFC ranges from 2 to 10%, depending on the definition. (2-4)

Clinical manifestation of CFC

CFC is a severe complication of CF, presenting itself in childhood with a peak incidence around the age of 10 years.(2,5) The diagnosis of CFC is often established based on routine, periodical ultrasound of the liver. CFC is associated with an irregular nodular pattern of the liver parenchyma, strongly indicative of the presence of cirrhosis.(6) Additionally, patients often develop clinical and biochemical signs of portal hypertension, like splenomegaly and thrombo- and leucocytopenia related to hypersplenism. Portal hypertension can be complicated by the development of gastrointestinal varices and variceal bleeding episodes.(7) Other complications of CFC include the development of ascites, hepatopulmonary syndrome and potentially hepatocellular carcinoma.(8,9) CFC is mainly characterized by a stable clinical course, presenting in pediatric age, with severe hepatic complications being rare.(10,11) *Koh et al.* recently reported that, probably as a result of the generally improved survival of CF patients, adult-onset CFLD may be more prevalent than previously assumed.(12) However, the development of end-stage liver failure is generally considered as a sporadic complication in CFC patients.(13) In case of progressive hepatic dysfunction, development of ascites and jaundice, intractable variceal bleeding or hepatopulmonary syndrome, liver transplantation should be considered in CFC patients.(14)

Mortality in CFC

There is controversy about CFC reducing life expectancy in CF patients. In the Cystic Fibrosis Foundation patient registry of 2016, it was reported that the primary cause of death in CF patients in the United States was related to hepatic causes in 2.7% (10/373).(15) In two separate publications, *Rowland et al.* and *Chyrssostalis et al.* reported the presence of severe liver disease as an independent risk factor for increased mortality in CF.(16,17) However, earlier publications from *Colombo et al.*, *Gooding et al.* and *Lindblad et al.* did not report CFC as a risk factor for early mortality.(3,4,18) It is also not clear, whether CFC patients primarily die due to liver failure or to

1 other CF disease complications (e.g., pulmonary failure). Although, in a recent study by Ye *et al.*,
2 reported that, based ON USCF Foundation Patient Registry data, two-thirds of deaths among
3 cirrhotic CF patients were pulmonary related.(7)
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7 *The Netherlands*

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9 In the Netherlands, during the observation period, medical care for CF patients was centralized in 8
10 certified medical centers with dedicated CF teams. Periodical, yearly, follow up including, among
11 other things, blood testing and liver ultrasound after the age of 5 years are included in the standard
12 of care in CF. Liver ultrasonographic screening and laboratory testing are used to screen for signs
13 of cirrhosis, portal hypertension, and hypersplenism. In the Netherlands liver transplantation for
14 CF-related liver failure or irreversible complication of CFC is an accepted indication for liver
15 transplantation, and liver transplantation is available for both children and adults.
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24 *Dutch CF Registry*

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26 The Dutch CF patient registry was initiated by the Dutch CF foundation in 2007. Anonymized
27 patient data is collected on a yearly basis, based on a standard set of variables of CF-related
28 disease and health issues. Patient information is collected and provided to the registry by all of the
29 8 Dutch care centers. Patient participation is voluntary and is only initiated after written informed
30 consent by the patient or their legal representatives. After a run-in period, in 2009, 98% of all CF
31 patients in the Netherlands participate in the Dutch CF patient registry.
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40 *Aim*

41 The aim of this study was to assess the prevalence of CFC in the Netherlands, to evaluate the role
42 of CFC on (early) mortality and analyze the cause of death. This information could help to provide
43 a risk assessment for patients and healthcare professionals, to improve medical care for CFC
44 patients and to develop strategies for early interventions.
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Methods

We performed a retrospective analysis of the prevalence, survival, and causes of death in CFC patients in all eight Dutch CF centers in the Netherlands during the period 1st January 2009 till 1st January 2015. The study was reviewed and approved by the local medical ethics review committee.

Subjects

CFC in our study was defined as a documented echogenic inhomogeneous liver with splenomegaly or documented histological diagnosis of cirrhosis. Splenomegaly was defined as a reported enlarged spleen at physical examination or an ultrasonographic measured spleen size above the 95th percentile for gender and age.(19) We identified all CFC patients in the 8 Dutch CF care centers alive at 1-1-2009, with a minimum age of 8 years. CFC patients were identified directly from medical chart review, on location, in the individual CF care hospitals, based on our described definition. In case of mortality in the period 1st January 2009 till 1st January 2015, we recorded age at death and retrieved the primary reported cause of death from the medical chart. In this study, we focus on the mortality risk of CFC. Patients who had undergone a liver transplantation at the start of the observation period were not included the study population.

We composed a control group, from Dutch CF patient registry data from patients aged 8 years and older at 1-1-2009. One of the collected variables in this database is 'liver disease', of which one optional answer is 'cirrhosis with portal hypertension/hypersplenism'. To compose the control group from CF registry, we excluded all patients recorded in the category 'cirrhosis with portal hypertension/hypersplenism'. From the control group, we retrieved data concerning age at death and survival in the period 1st January 2009 till 1st January 2015. 11 control patients (1.2%) were lost to follow-up during the observation period.

For both CFC and control patients, we obtained lung function parameters in the year 2009 (FEV1%: as the best registered forced Expiratory Volume in the 1st second as percentage of predicted value for age, height and gender (*based on: Global Lung Function Initiative 2012*) and parameters of nutritional status (patients < 18 years: Z-score for body mass index, ≥ 18 years: body mass index).(20)

1 *Statistical analysis*

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3 Statistical analysis was conducted using SPSS version 22.0. A log-rank test was used to compare
4 survival over the 6-year study period between the two groups. Survival data were plotted using the
5 Kaplan-Meier method. Lung function parameters, growth parameters and the median age at death
6 were not normally distributed and are therefore presented as median with interquartile range (IQR:
7 25th percentile – 75th percentile) and analyzed with the Mann–Whitney U test. A P value <.05 was
8 considered statistically significant.
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Results

Baseline patient characteristics,

From the medical chart review, we identified 103 patients that met our CFC definition on January 1st, 2009. In two patients CFC was proven by liver histological. Eight patients had previously undergone liver transplantation and they were excluded from the analysis regarding the median age of death and survival rate.

The control group, without CFC, consisted of 980 CF patients older than 8 years of age. Based on these findings we determined a prevalence of CFC among CF patients, older than 8 years of age, on 1st January 2009, in the Netherlands (including patients who underwent liver transplantation for CFC) of approximately 10% (103/1083).

Demographic data regarding gene mutations and gender of study population and controls are presented in *Table 1*. In the CFC group, there was a significantly higher incidence of patients homozygous for the F508 del mutation. There was no difference in gender distribution between CFC and control patients groups. The median age at baseline was significantly lower in the CFC group compared to the control group (18.8 vs. 22.4 years, $P < .01$). We found that all identified CFC patients were treated with ursodeoxycholate (UDCA). There was a significantly higher proportion of CFC patients that were reported to use pancreas enzyme replacement therapy; an indication of a higher prevalence of exocrine pancreatic insufficiency in this population. There was a trend towards a higher representation of CF-related diabetes in the CFC group, however, the difference was not significant ($p = 0.06$).

In children (8-18 years), we found no significant differences in standard deviation scores for weight for age (< 18 years) and best annual reported FEV1% at baseline. In adults, we did not find significant differences in BMI and/or lung function parameters (FEV1%) in CFC patients compared to control patients at the start of the observation period.

Lung transplantation

At baseline 3 (3%) CFC and 44 (4%) control patients had already received a lung transplantation. 10/95 CFC patients (10%) and 40/980 control patients (4%) underwent lung transplantation (odds-ratio 3, 95% CI 1-5, $P < .01$) during the 6-year study observation period.

Liver transplantation

During the study observation period, two patients received a liver transplantation. One patient was transplanted (at age 20 years) because of acute-on-chronic liver failure after a lung transplantation. One other patient received a liver transplant (at age 19 years), because of chronic liver failure (including the development of ascites). Both patients were alive at the end of our study observation period.

Survival

The 6-year survival rate in the period 1st January 2009 – 1st January 2015, was significantly lower in the CFC group compared to the control group (77% vs. 93%, $P<.01$). The Kaplan-Meier survival curves are shown in Figure 1. The hazard-ratio for 6-year mortality was 4 (95% CI: 2-6) in CFC patients compared to control patients.

Age at death

The median age at death was significantly lower among the deceased CFC patients (27 years, $n=22$) compared to deceased CF patients without CFC (37 years, $n=63$, $P=.02$, Table 2). We found a more than twofold higher percentage of deceased people in the age range <25 years in the CFC group, compared to the control group (45 vs. 17%, $P<0.01$).

Causes of death

We analyzed the reported causes of death of the 22 deceased CFC patients (Table 3). We found that pulmonary failure was reported as the primary cause of death in 15 (68%) cases and that liver failure was only reported as the primary cause of death in 4 (18%) cases. One 24-year old patient died due to end-stage liver failure after a refusal of liver transplantation. Three other patients (14%) died after a reported episode of acute-on-chronic liver failure following surgical procedures: 2 patients after abdominal surgery for distal intestinal obstruction syndrome (DIOS) and one patient following an isolated lung transplantation. In none of these 3 patients, liver transplantation was a feasible option at the time of liver failure. When looked at lung function tests data of deceased CFC patients during the follow-up period, we did not find any rapid decline in lung function tests, in particular also not in the CFC patients that, reportedly, died from respiratory failure. Furthermore, median BMI did not differ between survivals and deceased patients in the CFC group (21 vs. 21 kg/m^2)

Discussion

We studied the effect of the diagnosis CFC on patient survival in the Dutch CF population. This retrospective multicenter analysis is based on a 6-year period (1st January 2009 - 1st January 2015) and included all CFC patients alive on 1st January, 2009 in the Netherlands. We report that in the Netherlands, the presence of CFC is associated with a significantly higher risk for early mortality and an approximately 10-year lower median age at death.

We found that the majority of CFC patients reportedly died of pulmonary causes as the primary reason for death. The same observation was recently reported by Ye *et al.*(7) They found, based on data from the Cystic Fibrosis Foundation Patient Registry in the United States, that, in a cohort of 943 cirrhotic patients, two-thirds of deaths were reportedly pulmonary-related. However, Rowland *et al.* reported in their study looking at CF-related liver disease that died or received a transplant 50% died from pulmonary causes and 50% from hepatic causes.(16) They also reported that cirrhotic CF patients who died or received a transplant during the year follow-up period had statistically significantly reduced BMI and pulmonary function at baseline compared to those who were still alive. We found no baseline differences in lung function nor nutritional status between CFC patients and controls.

Based on study and results, no causal explanation can be given for the relation between CFC and the decreased survival and the younger median age at death of these patients. We hypothesize that CFC could be an associative risk factor for mortality in situations of pulmonary exacerbation or other forms of acute clinical deterioration. Indirect support for this hypothesis can be derived from a study by Chyrissostralis *et al.*(17) They described, based on a 15-year follow up study, that liver disease in CF is associated with lower rates for lung transplantation-free survival (Hazard-ratio 2.6, $p < .01$). Another explanation could be that the increased mortality is related to a worse nutritional condition described e.g. in cystic fibrosis-associated liver disease. Corbett *et al.* reported that children with established cystic fibrosis-associated liver disease have impaired growth and nutrition, and altered body composition.(21) In a recent France study patients with severe CFLD were reported to have worse lung function and nutritional status than other CF patients.(22) However, in our study population, we did not find a baseline difference in body weight and BMI in CFC patients

1 compared to controls. Our observations therefore do not provide support for improving dietary
2 care in CFC patients as a measure to prevent the increased mortality in these patients.
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4 The increased mortality among CFC patients was particularly striking in the young age group
5 of patients below 25 years. Even in this young age group, the primary reported cause of death
6 is related to pulmonary failure. The median age at baseline in the CFC patients was lower
7 compared to controls. We think this lower median age can be explained by an already
8 preexisting early mortality in CFC patients, before the start of our observation period (in 2009).
9 Increased existing early mortality in the CFC group will decrease the median of the compared
10 to controls.
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18 The mechanism of how the presence of CFC could affect pulmonary conditions in CF is not
19 well understood. Hepatopulmonary syndrome (HPS) is a well-described pulmonary
20 complication of CFC in general.(23) *Breuer et al.* described two CFC patients with
21 hepatopulmonary syndrome who had hypoxemia. (9) They suggested that HPS is
22 underdiagnosed in patients with CF because of their respiratory morbidity, which could lead to
23 hypoxemia. These findings underline the need to be aware of hepatopulmonary syndrome in
24 CFC patients in general and regularly check for platypnea/orthodeoxia. However, in our
25 current study population, no HPS was described, and none of the CFC patients in this series
26 was transplanted because of HPS.
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38 Three of the deceased CFC patients died due to a reported situation of acute-on-chronic liver
39 failure following a (non-hepatic) surgical procedure. Furthermore, one patient underwent liver
40 transplantation because of the development of acute-on-chronic liver failure after surgery. To
41 our knowledge, a correlation between surgery in CFC and mortality has not yet been reported.
42 These findings suggest that a surgical (and/or anesthesiological) procedure could be a
43 potential risk factor for acute-on-chronic liver failure in CFC patients. The pathophysiological
44 mechanism behind this observation is not yet understood but never the less underlines the
45 need for awareness in comparable clinical situations and surgery.
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56 The timing of liver transplantation for CFC patients remains an unresolved clinical
57 dilemma.(24) Most CFC patients, different from other liver disease, will not develop the classic
58 sequelae of end-stage liver disease. Moreover, based on our current finding, they reportedly
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1 primarily die due to pulmonary failure and not hepatic decompensation. It is unclear if early or
2 preemptive liver transplantation, in CFC patients without liver function decompensation, will
3 prevent early mortality or increase their survival. Liver transplantation as a treatment option
4 has its own risks. *Black et al.* reported, based on data from the United Network for Organ
5 Sharing database that liver transplantation in cystic fibrosis is associated with poorer long-term
6 patient survival compared to non-cystic fibrosis patients.(25) A survey among European CF
7 centers shows that many hospitals perform liver transplantations in CFC patients before the
8 development of end-stage liver disease.(26) The reported indications for transplantation were
9 hypersplenism, malnutrition, esophageal bleeding, and worsening lung function. The survey
10 also showed that there is still a debate regarding the timing of transplantation in relation to the
11 development of liver disease and liver function. Currently, in the Netherlands, liver
12 transplantation for CFC is generally performed only upon clinical signs of liver failure, e.g.,
13 synthesis or detoxification disorders or development of hepatopulmonary syndrome. We do
14 not know if this policy is related to our findings of decreased survival and lower median age at
15 death. The prognosis of preemptive liver transplantation in CFC patients without liver function
16 decompensation in comparison vs. no liver transplantation in this population is not known and
17 support for preemptive liver transplantation cannot be concluded based on our study or result.

18 We feel our results are relevant and important there, however, are some limitations to our
19 study may be addressed. Although, we performed a nationwide study, numbers of patients are
20 still limited. The data extraction, in particular, the recording of the primary cause of death, from
21 the medical charts was performed in a retrospective manner. By using a strict and objectifiable
22 definition of CFC we have tried to uniform the study group. The quality of the data in the Dutch
23 CF patients registry depends on the interpretation and input of the individual CF care centers.
24 We compared lung function and growth parameters of the study groups at baseline. In the
25 CFC patients that died, during the observation period, we did see a remarkable decline in lung
26 function or nutritional status. However, we did not have the opportunity to compare lung
27 function or the nutritional status of the complete study groups during the observation period.
28 Therefore we cannot adjust for the potential confounding effect of the deterioration in lung
29 function or nutritional status over time that might explain the worse survival in the CFC group.
30 To be able to study the cause of the decreased survival and lower median age of death in our
31 CFC population a long-term prospective study is indicated.

1 In conclusion, our study, based medical chart review and data from the Dutch CF patient
2 registry, showed that presence of CFC is associated with a 10-year lower median age at
3 death, in a country with centralized CF health care and the general availability of liver
4 transplantation. Most CFC patients primarily died pulmonary failure and not hepatic failure.
5 The cause or causes of decrease survival and lower median age at death in CFC patients are
6 not known. However, we feel, given the severity of the difference in survival, additional
7 awareness of the increased mortality risk, for instance in a situation of pulmonary
8 deterioration, is vital for this particular CF patient population.
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Conflict of interest

There is no conflict of interest

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Tables

Table 1. Baseline patients characteristics 1st January, 2009

		CFC	CF without cirrhosis
N		95	980
Male		52 (55 %)	539 (55%)
Age at start (years): median (IQR)		19 (15 – 25)	22 (15 – 34)*
Use of pancreas enzymes			
- yes		95 (100%)	767 (78%)*
- no		0 (0%)	198 (20%)
- unknown		0 (0%)	15 (2%)
CF-related diabetes			
- yes		24 (25%)	262 (27%)
- no		71 (75%)	520 (53%)
- unknown			198(20%)
<u>CFTR gene mutations</u>			
Homozygote F508del		59 (62%)	505 (52%)*
Heterozygote F508del		25 (26%)	358 (37%)*
Other mutations		9 (9%)	83 (8%)
Unknown		3 (3%)	34 (3%)
<u>Baseline lung function</u>			
FEV1%(median, IQR)	< 18 years	85 (72.0 - 92.9)	88 (77.4 - 97.5)
	> 18 years	62 (45.6 – 77.0)	61 (43.3 – 80.9)
FVC%(median, IQR)	< 18 years	90 (79.6 - 104.3)	93 (84.8 - 100.9)
	> 18 years	76 (62.9 – 86.1)	79 (64.6 - 89.6)
<u>Baseline nutritional status</u>			
Z-score weight for height (SD)	< 18 years	0.0 (-0.6 - 0.3)	-0.1 (-0.7 - 0.4)
BMI (median, IQR)	> 18 years	21 (19 – 23)	22 (20 – 23)

medians with interquartile range (IQR: 25th percentile – 75th percentile)

*P value <.05 was considered statistically significant(Mann–Whitney U test)

FEV1:forced expiratory volume in 1 second

FVC: forced volume vital capacity

BMI: Body mass index

Table 2. Age of death and proportion of death per age category

	CFC	CF without cirrhosis
Deceased patients	22	63
< 25 years	10 (45%)	11 (17%)*
25-40 years	8 (36%)	28 (44%)
> 40 years	4 (18%)	24 (38%)*
Median age at death (years)	27(18 - 38)	37 (27-45)*

*P value <.05 was considered statistically significant(Mann–Whitney U test)

Table 3. Distribution of reported cause of death in deceased CFC patients

	N (%)
Pulmonary failure	15 (68%)
Multi-organ failure (unknown origin)	1 (5%)
Liver failure	4 (18%)
Non-CF related cause	1 (5%)
Unknown cause	1 (5%)
Total	22

Figures

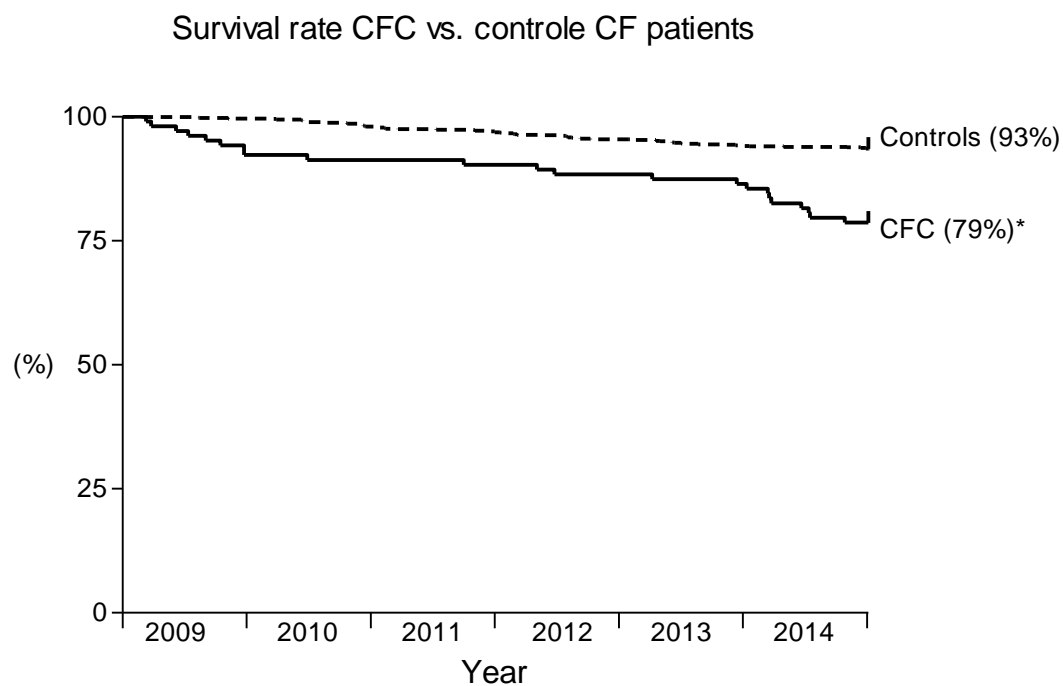


Figure 1. Survival rate CFC vs. control CF patients

Kaplan-Meier curve showing the 6-year survival of CFC-patients compared with CF patients without CFC in the period 1st January, 2009 till 1st January, 2015. The 6-year survival rate in the CFC group was significantly lower compared to the control group ($P < 0.01$).